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Brief Clinical Report

Another Arab Patient With Overlap of Váradi-Papp/Opitz Trigonocephaly Syndromes?

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We describe a Bedouin boy with multiple congenital anomalies/mental retardation (MCA/MR). He has frontal bossing, ridged metopic suture, bilateral ptosis, right squint, depressed nasal bridge, small nose, anteverted nostrils, lobulated tongue, polydactyly of both hands, microphallus, hypoplastic scrotum, microtestes, dysgenesis of corpus callosum, and a Dandy-Walker variant. This phenotype overlaps both the Varadi-Papp syndrome (OFD VI) and Opitz trigonocephaly (C syndrome). This phenotypic overlap is discussed in light of the concept of splitting and lumping in genetic diseases. Am. J. Med. Genet. 68:54–57, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: OFD VI; Opitz trigonocephaly; overlap; Arabs

INTRODUCTION

In 1980, Váradi et al. delineated a new oral-facial-digital syndrome in an inbred Gypsy population with reduplication of halluces, central hexadactyly, cleft lip/palate, lingual nodules, and somatic/psychomotor retardation. Münke et al. [1990] presented clinical/MRI evidence for hypoplastic cerebellar vermis as a consistent part of that syndrome, which was then referred to as oral-facial-digital syndrome type VI (MIM 277170). Other important traits that differentiate the Váradi-Papp syndrome (OFD VI) from different OFD types [Temtamy and McKusick, 1978; Gorlin et al., 1990] include Dandy-Walker malformation, feeding difficulty, and some hypothalamic manifestations, e.g., bulemia and hyperthermia [Toriello et al., 1993].

In 1969, Opitz et al. described a brother and a sister with another malformation syndrome (C syndrome or Opitz trigonocephaly, MIM 211750), comprised of microcephaly, ridged metopic suture, trigonocephaly, squint, short small nose, depressed nasal bridge, anteverted nostrils, high arched palate, low-set posteriorly angulated ears, cryptorchidism, prenatal short stature, mental retardation, and hypotonia.

Recently, Cleper et al. [1993] described overlapping manifestations of Váradi-Papp and Opitz trigonocephaly syndromes in two Arab cousins. Herein, we report another Arab patient with signs of both syndromes. The implications of this phenotypic overlap are discussed in light of the concept of splitting and lumping in the nosology of genetic diseases [McKusick, 1969].

CLINICAL REPORT

This boy was born in September 1993 to second-cousin healthy Bedouin parents who had four healthy children and a stillborn boy with unspecified multiple congenital anomalies. Birth weight was 3,300 g, length was 51 cm, and head circumference (OFC) was 36.6 cm. Apgar score was 9 and 10 at 1 and 5 minutes, respectively. The baby was incubated for 17 days because of aspiration pneumonia. He was found to have multiple congenital malformations with a prominent forehead, ridged metopic suture, visual loss, slight up-slant of the palpebral fissures, bilateral ptosis, right divergent squint, right nystagmus, clear corneae and lenses, sluggish pupillary reactions, and normal optic disks and retina. He had depressed nasal bridge, a small nose, anteverted nostrils, down-turned upper lip, lobulated tongue with multiple nodules at the edge, and apparently low-set posteriorly angulated ears. On the left hand he had two extra, fused post-axial digits, interdigital (4/5) polydactyly with a hypoplastic extra finger between the right 4th and 5th digits, and a hypoplastic third toe of the right foot. The baby was hypotonic and had microphallus, microtestes, and hypoplastic scrotum (Fig. 1). Clinical assessment at the age of 1½ years showed that his length was 67.5 cm (<3rd centile), weight was 6,000 g (<3rd centile), and OFC was 44 cm (<−2 SD). He had failure to thrive, retarded psychomotor development, and repeated gastro-oesophageal

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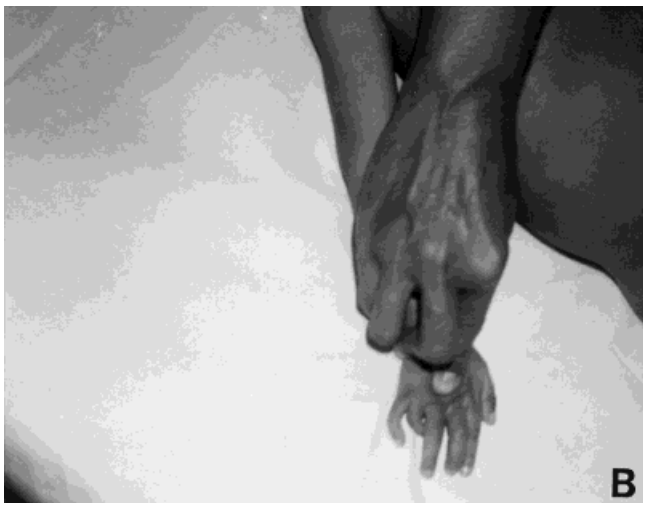

Fig. 1. **A, B, C:** The patient at age 1½ years.

reflux with frequent chest infections. He could not walk or crawl and could only sit with support. He had reduced hearing and could not see. He had a hypotonic head, diminished reflexes and, plantar flexor response.

Skeletal survey at the age of 1½ years showed that the skeleton was generally small for age. There was no significant disproportion or abnormal shape of the bones and no substantial delay in ossification. The skull showed an open anterior fontanelle with frontal bossing. No ossification centre was seen in the anterior arch of the atlas. Both hands showed polydactyly with a short wedge-shaped "metacarpal" bone between the fourth and fifth metacarpals of the right hand with a shorter digit consisting of three phalanges (Fig. 2) and brachymesophalangy of the right fifth finger. The left hand showed two abnormal digits at the ulnar side with two irregular skeletal elements (Fig. 2). The feet contained five toes each, with only two phalanges in the right third toe.

No abnormal abdominal ultrasound findings were detected. Brainstem-evoked-potential-audiometry (BEPA) was conducted and although brainstem evoked potentials were within normal limits, BEPA hearing threshold was reduced for both ears, being at 50 dB HL for the left ear and 60 dB HL for the right ear (normal value for his age is at 20 dB). Electroencephalogram was abnormal. Head ultrasound and fine slice axial scanning showed moderate widening of the lateral ventricles, accentuated anterior part of interhemispheric fissure, an irregular interhemispheric cyst with partial absence of corpus callosum, a large posterior fossa, and an ill-defined tentorial notch. The fourth ventricle was enlarged with widening of vallecula, absence of the lower part of cerebellar vermis, large cisterna magna and hypoplastic medulla oblongata, findings highly suggestive of a Dandy-Walker anomaly (Fig. 3). Barium swallow and meal demonstrated a wide oesophagus, a free

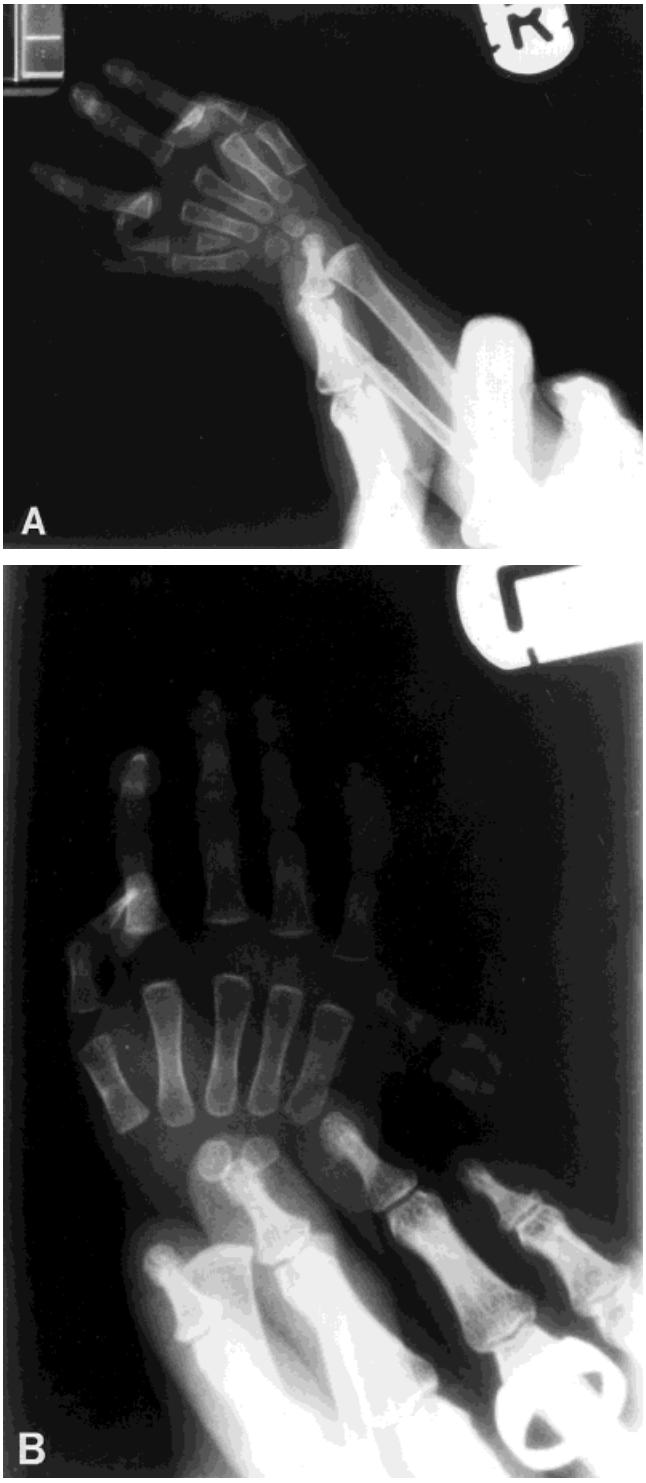

Fig. 2. Radiogram of the right (**A**) and left (**B**) hands of the patient (viewed from the palmer side).

cardia situated under the diaphragm, an organo-axial volvulus of the stomach, a free gastric outlet, and a normal duodenum with a normal position of duodeno-jejunal flexure. As stated before, the child had gastro-oesophageal reflux, with repeated vomiting, recurrent chest infections and failure to thrive. He had a normal karyotype (46,XY).

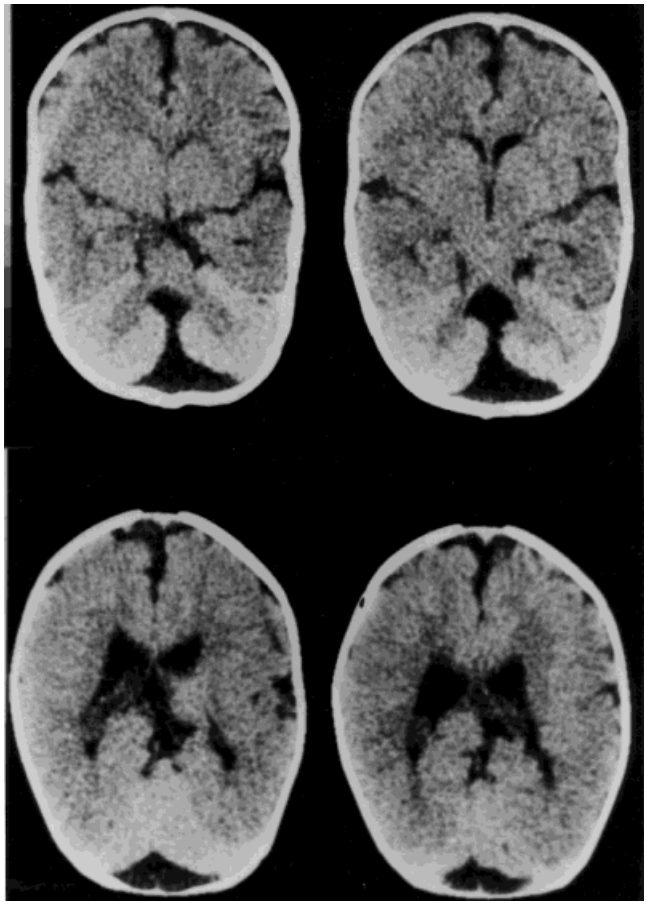

Fig. 3. CT scan of the patient.

DISCUSSION

The syndrome in the present case is similar to the Váradi-Papp (OFD VI) syndrome on the basis of feeding difficulty, tongue lobules/nodules, postaxial polydactyly of the left hand, "central" polydactyly of the right hand, and corpus callosum hypoplasia, in addition to the demonstrated abnormalities of posterior fossa that are compatible with a Dandy-Walker variant (Table I). Also, the present phenotype shows a considerable overlap with Opitz trigonocephaly (C syndrome), in terms of the presence of ridged metopic suture, retarded global development, and the presence of a small nose with depressed nasal bridge (Table I). Signs common to both OFD VI and C syndrome include the small penis and testes, short stature/failure to thrive, strabismus, ear abnormality, and hypotonia.

The present case bears a great similarity to the phenotype described previously in two Arab cousins with frontal bossing, ridged metopic suture, strabismus, anteverted nostrils, depressed nasal bridge, ear abnormality, central polydactyly, microphallus, microtestes, and feeding difficulty [Cleper et al., 1993]. It is clear that the present case, like the previously described cousins, fits the Váradi-Papp/Opitz trigonocephaly overlap phenotype (Table I).

TABLE I. Comparison of the Overlapping Phenotypes With Manifestations of Váradi-Papp (OFD VI) and Opitz Trigonocephaly (C Syndrome)*

Trait	Present case	Cleper et al. case 1	1993 case 2	OFD VI	C syndrome
MIM [McKusick, 1994]				277170	211750
Mental/developmental retardation	+	+	?	±	+
Ridged metopic suture	+	+	−	−	+
Palpebral fissure slant	Up	Up	Down	−	Up
Epicanthus	−	+	+	+	+
Strabismus	+	+	?	+	+
Anteverted nostrils	+	+	+	−	+
Depressed nasal bridge	+	+	+	Broad	Broad
Ear abnormalities	+	+	+	+	+
Buccal franula/tongue lobules	+	+	+	+	+
Cleft palate	−	+	−	+	High
Wide alveolar ridge	−	+	+	+	−
Cardiac anomalies	−	+	+	+	+
Polydactyly	Cen/ post	Cen	−	Pre/ post/ cent	Post
Camptodactyly	−	−	+	−	−
Interdigital webbing/syndactyly	+	+	+	+	+
Short tapering fingers	−	+	+	+	+
Micropenis	+	+	+	+	+
Cryptorchidism	+	+	+	+	+
CNS defects	Cereb/ cal/ mc	Cal	−	Cereb	Mc
Hypotonia	+	+	+	+	+
Feeding difficulty	+	+	?	+	−
Bulemia/obesity	−	+	?	+	+
Joint contracture	−	+	−	+	+
Neonatal death	−	−	+	±	+

* pre, preaxial; cen, central; post, postaxial; cereb, cerebellar; cal, callosal; mc, microcephaly.

The condition in this patient and in the previously reported Arab cousins [Cleper et al., 1993] raises the question as to whether this concurrence phenotype represents a single genetic entity or a new syndrome?

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